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FILING DATE: ***August 21, 2003***

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

60/496884
08/21/03

INVENTOR(S)		
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TITLE OF THE INVENTION (280 characters max)

Methods and Spectra for Monitoring Fetal Growth and Predicting Infant Birth Weight

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 17 ☐ CD(s), Number

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☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

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☒ Payment by credit card. Form PTO-2038 is attached.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

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Date 8/21/03

REGISTRATION NO. *(if appropriate)* 38,350

Docket Number: MGU-0017

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1) Patent Application Transmittal Letter (in duplicate);

2) Application consisting of 17 pages of specification, including 3 page of claims and 1 page of abstract;

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Kathleen A. Tyrrell

MGU-0017 PATENT

Methods and Spectra for Monitoring Fetal Growth and Predicting Infant Birth Weight

Predictors of Birth Weight

PROBLEM: The assessment of fetal birth weight forms an important part of prenatal care. Therefore accurate early determination of fetal weight prior to delivery could markedly improving perinatal outcomes. Thus the need for a quick and easy method for estimating fetal weight in-utero particularly infants at risk of for either of the two extremes: (1) macrocosmia (also referred to as large for gestational age or LGA) or (2) small for gestational age (SGA) or intrauterine growth retarded (IUGR).

Currently the most reliable predictor of infant birth weight is ultrasonography where according to a recent review article is capable of predicting birth weight to within 300 to 400 grams (Table 12, Nahum eMedicine Journal), but the authors cited that this as well as other techniques still have significant degrees of inaccuracy and suggested that a reasonable strategy for arriving at estimated fetal weight is STILL to use multiple estimates based on different sources of clinical and sonographic information. Moreover they noted that even with ultrasound, macrosomia is not easily predicted. Both ultrasonography and clinical palpation of fetal size have sensitivities of less than 60% for the prediction of macrosomia with false positives far greater than 40%. Likewise for small fetuses less than 1800 grams ultrasonic fetal weight estimates are often in error by as much as 25%. The disadvantages of ultrasonography include the complicated and labor intensive nature of the methodology that is often limited by the suboptimal visualization of fetal organs. It also requires costly equipment and highly trained personnel. This later issue often precludes use of any of this methodology in developing countries.

SOLUTION: Our patent focuses on the use of Raman spectral analyses to identify a series of 8-12 biochemical markers in amniotic fluid that are predictive of infant birth weight. Advantages of our approach are (1) that it requires a single sample of a small volume of amniotic fluid (uL) to measure all important biochemical components simultaneously and thus importantly preserves their chemical properties within the fluid matrix of amniotic fluid, which in and of itself is important barometer of fetal health as either too little (oligiohydramniois) or too much (polyhydramniois)is a fetal health risk. It overcomes limitations of other chemical techniques that require single analyses of individual components, which not only are susceptible to concentration differences if volume is perturbed, but to lack of techniques to measure components in this new compartment for which assays in small volumes have not yet been developed. However more importantly, our Raman spectral analysis is accurate to within 100 to 400 grams of final birth weight when performed as EARLY as 15 wks gestation!!! This thus provides the first medical possibility of early in-utero diagnosis of SGA and LGA.. Moreover the methodology can be performed at the time of routine amniocentesis and does not require additional involved chemical processing. The application of this novel technique can be easily applied in the hospital, clinic and field setting with the development of two machines: one requiring use of a small portable Raman machine to measure amniotic fluid droplets at the time of collection of 'fresh samples' for immediate bedside processing and (2) the development of a vaginal or tummy fibre optic probe to be used non invasively throughout the course of pregnancy providing for the first time a means to collect series measurements and to monitor in- utero fetal growth and development sequentially Cost is affordable making the possibility of more widespread use of amniotic fluid for routine fetal monitoring and with an accuracy far exceeding current techniques.

Our current activities have identified several components. These include but are not limited to glucose, insulin, 2 IGF – binding proteins, several amino acids, and two metabolic acids (lactic acid and uric acid). Currently additional promising components include nitric oxide and several fatty acids including the trans fatty acids which are only found in highly hydrogenated food products and that could in fact limit the use of the essential fatty acids required for fetal growth.

Amniotic Fluid NIR-RAMAN Spectroscopy

Amniotic fluid from 68 women at 14-16 weeks gestation, were measured. All patients signed Mcgill University a Human Subjects Approved form for consent. After genetic testing, all remaining amniotic samples were stored frozen. Near Infrared Raman spectral were obtained using a Bruker Fourier Transform Near Infrared Raman Spectrometer. Each amniotic fluid sample was taken from the freezer and warmed to 20 C. Samples were then transferred into a 2 mm diameter glass tube which and placed into the Raman system. The Raman system was maintained at 20+/- 1 C during the course of the experiment. A Nd:YAG laser emitting at 1064 nm was focused onto the amniotic fluid samples. Raman shifted scattering from the samples was collected by the FT-spectrometer and detected using a cooled NIR detector. The spectra were scanned at 1/sec resulting in an 8 cm-1 resolution of shift from 0-3750cm-1. A total of 1800 scans were averaged for each sample. After a Fourier Transform of the raw interferogram, the data was stored as 1919 data points spanning the 0-3750 cm-1 spectral range.

Data Preprocessing.

The amniotic fluid RAMAN spectra were preprocessed to reduce the effects of intensity variations of the laser. In particular, each spectrum was normalized to the Raman emission of the Si-OH at 2500cm-1. Likewise, spectra were smoothed with a 15-point moving average boxcar smoothing function to reduce spurious noise in the measurement.

Haar Transform

The Haar transform (HT) is the oldest form of wavelet analysis.[15-27] It projects a given signal onto an orthogonal set of basis functions. Data contained in a time window of $0 < \tau < 1$ is decomposed according to a father wavelet $\phi(\tau)$, a mother wavelet $\psi(\tau)$ and a series of daughter wavelets $\psi_{n,k}(\tau)$, where n and k determine scaling and translation respectively:[31]

$$\phi(\tau) = \begin{cases} 1 & \text{if } 0 \le \tau \le 1 \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

$$\psi(\tau) = \begin{cases} 1 & \text{if } 0 \le \tau \le \frac{1}{2} \\ -1 & \text{if } \frac{1}{2} \le \tau \le 1 \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

$$\psi_{n,k}(\tau) = \psi(2^n\tau - k), \quad 0 \le k \le 2^n - 1 \tag{3}$$

Likewise, each daughter wavelet can be decomposed into the sum of two son wavelets, $\phi_{nk}(\tau)$, with a corresponding positive and negative weighting with the associated scaling and translation. It is interesting to note that all daughter wavelets can be decomposed into a sum of son wavelets, i.e. compressed and shifted versions of the father wavelet. For instance, $\psi = \phi_{1,0} - \phi_{1,1}$. Thus, the HT can be carried out with a basis set composed only of zeros and ones, which can be implemented experimentally by spectral filters. To determine the wavelet coefficients, it is useful to represent the wavelets by a matrix. For example, the father, mother and first generation of daughter wavelets can be written as A_2:

$$A_2 = \begin{array}{c} \begin{matrix} \phi(\tau) & \psi(\tau) & \psi_{1,0}(\tau) & \psi_{1,1}(\tau) \end{matrix} \\ \begin{bmatrix} 1 & 1 & 1 & 0 \\ 1 & 1 & -1 & 0 \\ 1 & -1 & 0 & 1 \\ 1 & -1 & 0 & -1 \end{bmatrix} \end{array} \quad (4)$$

where each column corresponds to a wavelet, and each row represents the Haar wavelet values when the time window is broken into 4 equal segments. Decomposing a Raman signal of 4 equal wavenumber bins into wavelet coefficients is thus reduced to the following matrix math problem: a coefficient vector must be calculated such that its multiplication to A_2 yields the Raman spectral profile. Wavelet coefficients in the resulting vector will be ordered starting from the lowest resolution wavelet (father wavelet) and progressing to higher spectral resolution. Matrix A_2 can be expanded to include further generations of daughter wavelets or son wavelets, thereby extending the analysis to higher frequency levels. More in-depth information on the Haar transform can be found elsewhere.[27, 31, 32]

Computing the Haar coefficients of the distributions collected experimentally using the FTNIR Raman instrument was the first step in the data analysis. The son wavelete Haar transform calculation was carried out by a custom program written in Matlab (The MathWorks Inc., Natick, MA) which iteratively calculated sums and differences. Computation required the length of the input data to be a power of 2 long. Coefficients for a maximum of 1024 Haar son wavelets were obtained, ordered from low resolution to high spectral resolution.

Stepwise Multilinear Regression.

Inverse least squares regressions can be used to estimate the extrinsic parameters of a given sample from the preprocessed Raman spectra. However, it is probable that not all 1024 wavelets are needed, since the HT gives a sparse representation of the signal. The stepwise multilinear algorithm is an established method of choosing the subset of variables most correlated to a quantity of interest.[33] The general goal of the genetic algorithm was to identify the combination of wavelets that best describes a given data set according to equation 5:

$$Y = \alpha_0 + \alpha_1 X_1 + \alpha_2 X_2 + \ldots + \alpha_n X_n \quad (5)$$

where Y is the dependent variable (Birthweight), $X_1, X_2, \ldots, X_n$ are independent variables (i.e. wavelet coefficients), and $\alpha_0, \alpha_1, \ldots, \alpha_n$ are the coefficients determined from a set of X's by inverse least squares regression. The combination of wavelets that best estimated Y were determined according to the following scheme:

1. Set the range of HT coefficients that the Stepwise uses.
2. Choose the number of wavelets to include in the model.
3. Evaluate the fitness of each model.
4. Repeat steps 2-4 with an increasing number of wavelets included in the model.
5. Choose the optimal number of variables.
6. Evaluate the model using an independent data set.
7. Repeat steps 1-6 changing the range of HT coefficients used by the Stepwise method.

1. **Setting the range of HT coefficients that the Stepwise MLR uses:** The goal of the STEPMLR was to determine a small subset of wavelets correlated to the birthweight. Likewise, low-resolution (large wavelength range) components were preferable in view of developing identifying spectral components associated with fetal development and for simplified instrumentation in the future. Thus, in addition to allowing the Stepwise method to choose amongst all Haar son wavelets to optimize the estimation, the algorithm was also run with only wavelets of spectral resolution lower than 512, 256,128, 64 and 32 waveletes.

2. **Choosing the number of wavelets to include in the model:** Start with one wavelet, i.e. one X in equation 5, and increase progressively. The maximum number of wavelets was set according to the number of wavelet coefficients available for Stepwise selection. In all cases the maximum number of wavelets to use was set to 10.

3. **Evaluating the fitness of each individual:** For each model in the population, the coefficients α_1 to α_n of equation 5 were calculated by inverse least squares regression using the calibration set with known values of absorption or scattering determined from sample preparation. Estimates of birthweight were obtained by applying equation 5 with the determined α_n parameters and the Haar coefficients of the test set, and a standard error of calibration (SEC) was calculated. Thus a smaller SEC was associated with a better model.

4. Repeat steps 2-3 with an increasing number of wavelets included in the model: The maximum number of wavelets was chosen in step 2.

5. Choosing the optimal number of variables: A prediction error sum of squares (PRESS) plot was generated by plotting SEC vs. the number of wavelets in the model. Let h designate the number of wavelets in the model with the minimum PRESS value. The model selected was the one with the fewest number of wavelets such that PRESS for that model was not significantly greater than PRESS for the model with h wavelets, based on an f-test at the 95% confidence level.[34]

6. Evaluating the model using an independent data set: The "optimal" model was evaluated by estimating the birthweight values of an independent data set, the validation set, with the calibration coefficients from the calibration set. R^2 and the coefficient of variation (C.V.) were used as indicators of the validity of the model.

Results.

Three separate calibrations were made for estimating birthweight from the amniotic fluid RAMAN Spectra. First, spectra associated with all of the samples were used to estimate the birthweight. The results are shown in Figure 1. Estimation of birthweight within 500 grams for all sample were achieved. Significantly better results were obtained when the samples were subdivided into groups from < 3500 grams and >3500 grams. Results of these two calibrations are shown in Figures 2 and 3. As can be seen, estimations with

approximately 200 grams error were found with only one outlier for each group. This is significantly better than any current method.

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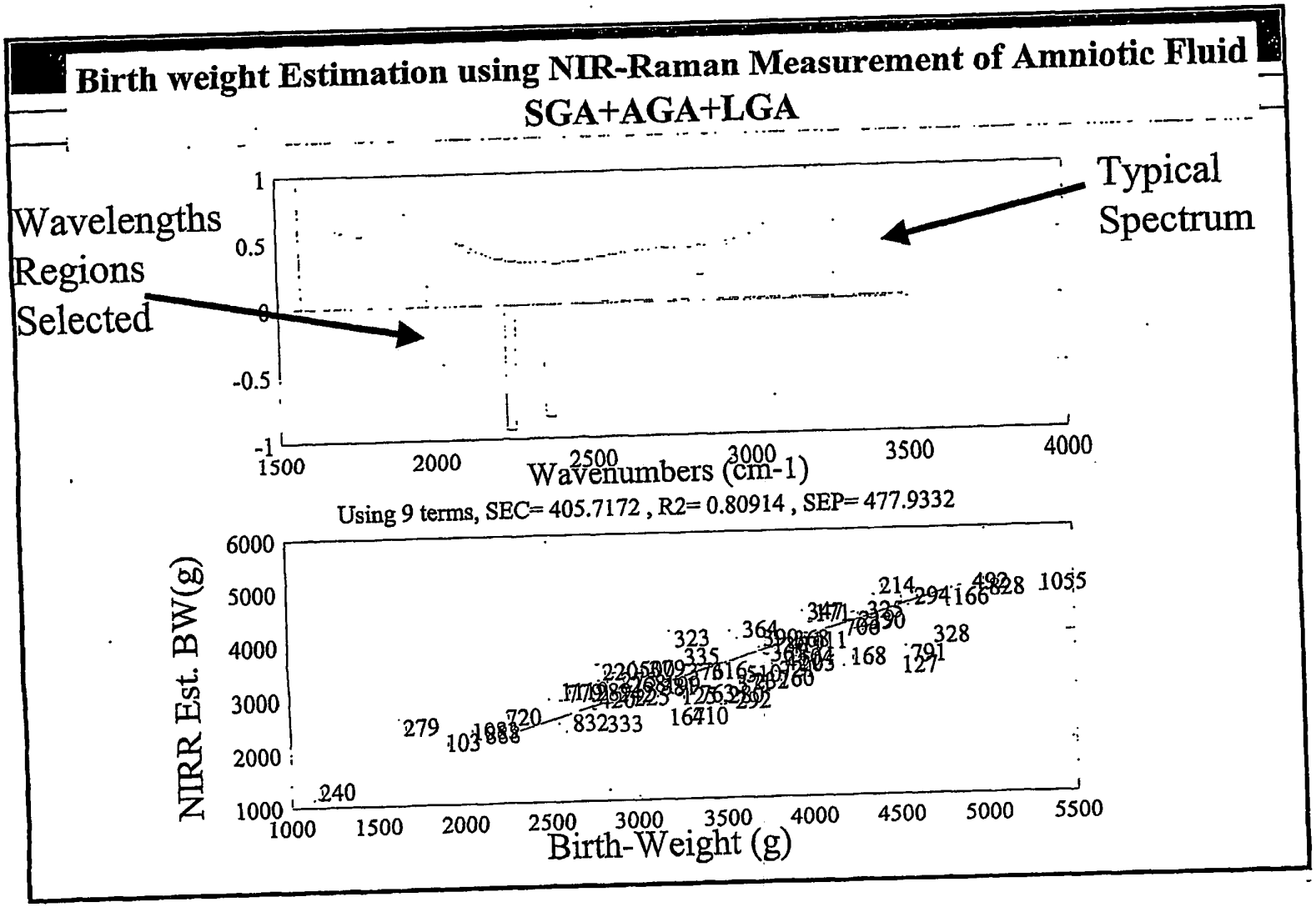
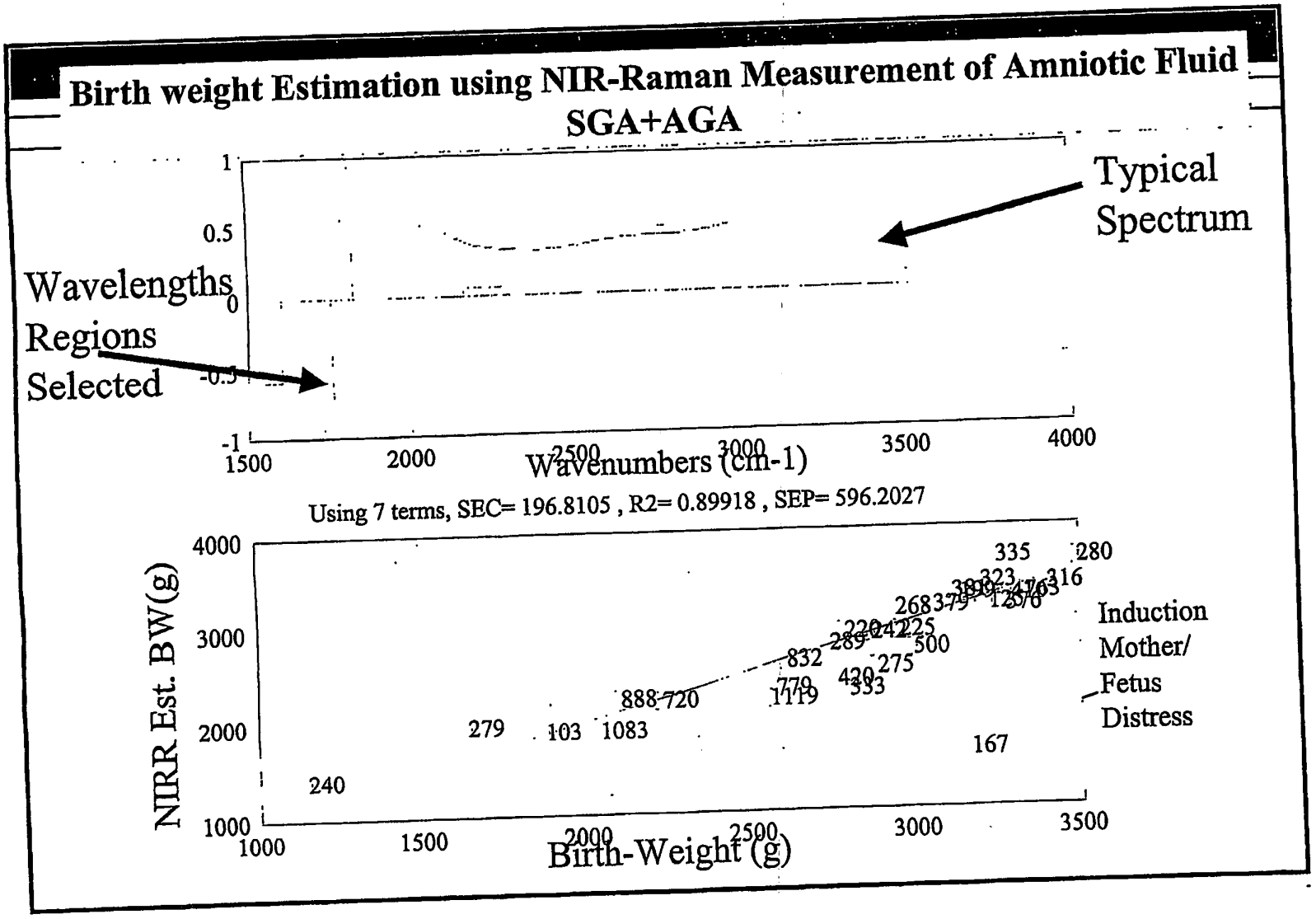
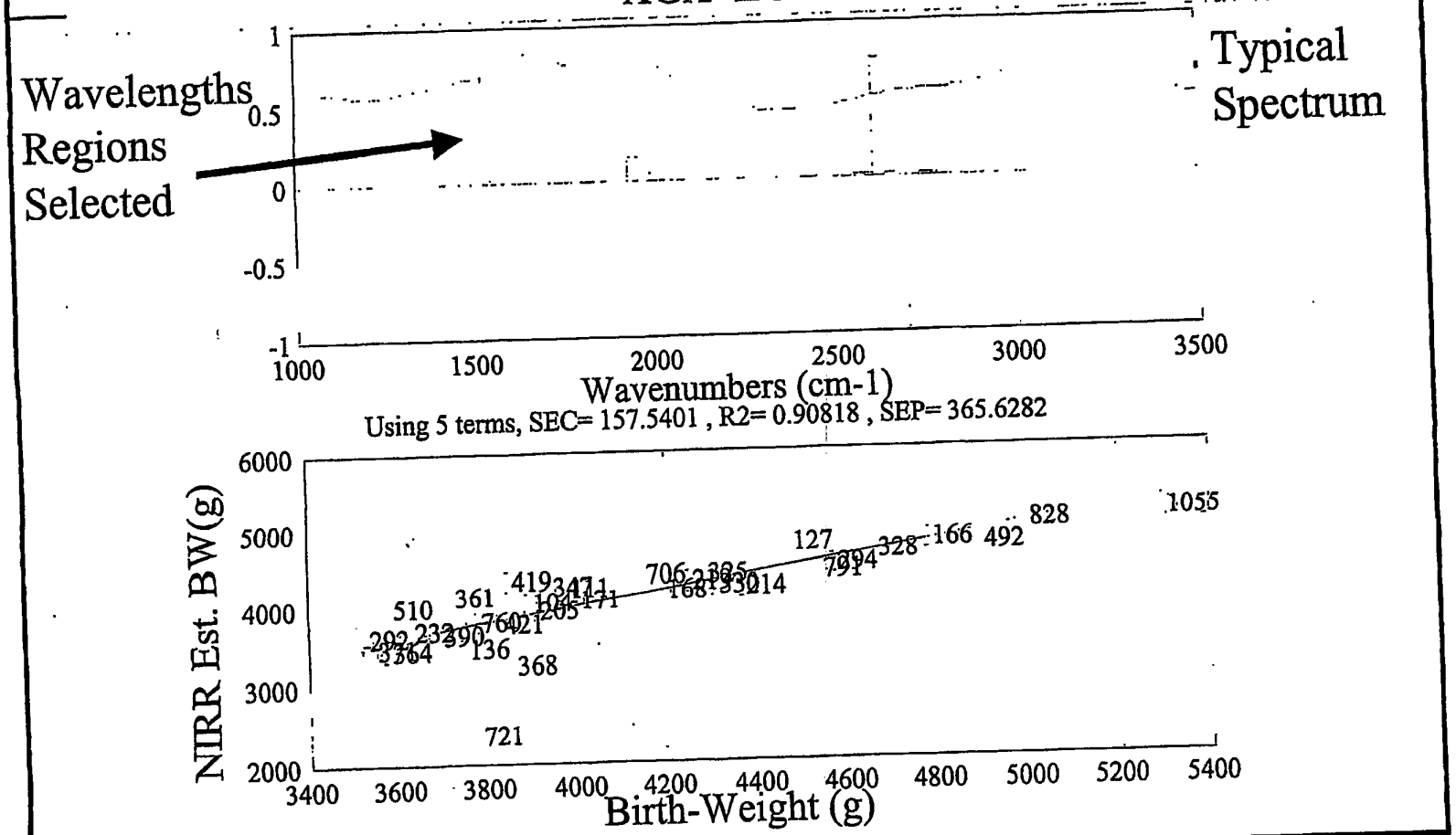

Birth weight Estimation using NIR-Raman Measurement of Amniotic Fluid
SGA+AGA+LGA
Wavelengths Regions Selected
Typical Spectrum
1
0.5
0
-0.5
-1
1500
2000
2500
3000
3500
4000
Wavenumbers (cm-1)
Using 9 terms, SEC= 405.7172 , R2= 0.80914 , SEP= 477.9332
NIRR Est. BW(g)
6000
5000
4000
3000
2000
1000
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
Birth-Weight (g)


Birth weight Estimation using NIR-Raman Measurement of Amniotic Fluid
SGA+AGA
Typical Spectrum
Wavelengths Regions Selected
1
0.5
0
-0.5
-1
1500
2000
2500
3000
3500
4000
Wavenumbers (cm-1)
Using 7 terms, SEC= 196.8105 , R2= 0.89918 , SEP= 596.2027
NIRR Est. BW(g)
4000
3000
2000
1000
1000
1500
2000
2500
3000
3500
Birth-Weight (g)
335
280
323
316
268
220
225
289
500
832
275
420
333
888
720
1119
279
103
1083
167
240
Induction Mother/ Fetus Distress

Birth weight Estimation using NIR-Raman Measurement of Amniotic Fluid

AGA+LGA



What is Claimed is:

1. A method for monitoring fetal growth and predicting birth weight of an infant prior to birth comprising measuring one or more selected biochemical markers in a sample of amniotic fluid obtained from a pregnant woman, wherein levels of the selected biochemical markers correlate with fetal growth and birth weight of the infant.

2. The method of claim 1 wherein the one or more selected biochemical markers in the sample of amniotic fluid are measured by a spectroscopic technique.

3. The method of claim 2 wherein the spectroscopic technique comprises Near Infrared spectral analysis, diffuse reflectance spectroscopy, Near Infrared Raman spectral analysis, or nuclear magnetic resonance spectroscopy.

4. The method of claim 1 wherein at least one of the selected biochemical markers comprises glucose, insulin, an IGF binding protein, an amino acid or a metabolic acid.

5. A method for monitoring fetal growth and predicting birth weight of an infant prior to birth comprising:

(a) isolating amniotic fluid from a pregnant woman;

(b) determining a level of one or more selected biochemical markers in the amniotic fluid obtained in step (a);

(c) generating a spectrum for levels of the one or more selected biochemical markers determined in step (b); and

(d) correlating the generated spectrum for the one or more selected biochemical markers with fetal growth or birth weight of the infant prior to birth.

6. The method of claim 5 wherein the amniotic fluid is

isolated from the pregnant woman invasively.

7. The method of claim 5 wherein the amniotic fluid is isolated from the pregnant woman non-invasively.

8. The method of claim 5 wherein at least one of the selected biochemical markers comprises glucose, insulin, an IGF binding protein, an amino acid or a metabolic acid.

9. The method of claim 5 wherein the one or more selected biochemical markers in the sample of amniotic fluid are measured by a spectroscopic technique.

10. The method of claim 9 wherein the spectroscopic technique comprises Near Infrared spectral analysis, diffuse reflectance spectroscopy, Near Infrared Raman spectral analysis, or nuclear magnetic resonance spectroscopy.

11. A method for simultaneous measurement of multiple constituents of amniotic fluid in a small volume of amniotic fluid isolated invasively or non-invasively from a pregnant woman, said method comprising analyzing amniotic fluid by a spectroscopic technique.

12. The method of claim 11 wherein the spectroscopic technique comprises Near Infrared spectral analysis, diffuse reflectance spectroscopy, Near Infrared Raman spectral analysis, or nuclear magnetic resonance.

13. A spectrum predictive of birth weight of an infant prior to birth derived from analysis of a sample of amniotic fluid of a pregnant woman comprising levels of one or more selected biochemical markers measured in the amniotic fluid.

14. The spectrum of claim 13 wherein at least one of the biochemical markers comprises glucose, insulin, an IGF binding protein, an amino acid or a metabolic acid.

ABSTRACT

Methods and spectra for monitoring fetal growth and predicting birth weight of an infant prior to birth are provided wherein one or more selected biochemical markers are measured in a sample of amniotic fluid obtained from a pregnant woman. Levels of the selected biochemical markers correlate with fetal growth and birth weight of the infant.